

California M E D I C I N E

OFFICIAL JOURNAL OF THE CALIFORNIA MEDICAL ASSOCIATION

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Volume 90

FEBRUARY 1959

Number 2

The Tuberculous Diseases

Originating from Different Species of Acid-Fast Bacilli

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• Disease due to the typical human type tubercle bacillus is rapidly diminishing as a result of public health measures and specific chemotherapy. Lesions in man resulting from other kinds of acid-fast bacilli are now being recognized in increasing numbers. Some of these bacilli had been seen before but were confused with typical *M. hominis*, others were considered to be harmless saprophytes, while others could not be found with the methods used. Special culture media, different conditions for cultivation, new physical, chemical and biological tests, and inoculation into a variety of animal hosts are now available. With their use more than a

dozen different strains of human type tubercle bacilli, and more than a score of other species of acid-fast bacilli may now be distinguished. A simple chemical test readily separates the human type tubercle bacilli from all other kinds of acid-fast bacilli. The differentiation of the different human and animal pathogenic acid-fast bacilli from the avirulent saprophytes and other harmless mycobacteria presents great difficulties, but methods are becoming available which usually make this possible. Since the distinction may be of great therapeutic and epidemiologic importance, the effort should be made.

TUBERCULOSIS is the oldest disease known to man but the terms used to designate it, and their meanings, have changed over the course of the centuries. Hippocrates and other ancient writers described under the name of *phthisis*, a disease characterized by thinning of the body and wasting fever, associated with cough and expectoration, pain in the chest, difficult breathing, rapid pulse, pallor, thirst, loss of appetite, flushed cheeks, winged scapulae, curved nails, diarrhea or constipation, insomnia and loss of voice.¹⁴

Several hundred years later Celsus, who retained the name *phthisis* for the pulmonary disease, translated the Hippocratic term *phyma*, meaning a nodular lesion in the skin, by the Latin *tuberculum*.⁷

Presented before the Section on Public Health at the 87th Annual Session of the California Medical Association, Los Angeles, April 27 to 30, 1958.

Sylvius later used the word *tuberculosis* to designate nodular lesions in the lung.³ This name was used increasingly thereafter to include a wide variety of pulmonary and extrapulmonary lesions characterized by the production of granulomatous masses or of caseous necrosis.¹⁹

The coexistence or succession of *phthisis* or pulmonary consumption with chronic laryngitis, enteritis, fistula in ano, miliary tuberculosis, meningitis, hydrocephalus, pleural effusion, scrofula, cold abscesses or chronic white swellings, lupus, Pott's disease or kyphosis and many other conditions was repeatedly noted. Their true relationship, however, was seldom suspected and diverse ideas as to etiology¹¹ were entertained. Following the discovery of the tubercle bacillus in 1882 its etiological significance in each of these various conditions led

to use of the name *tuberculosis*¹⁵ for all of them.

Since the time of Robert Koch the word *tuberculosis* has lost its original significance and has come to indicate any disease which might be caused by the tubercle bacillus. The words *tuberculous* and *tuberculosis* were indeed restricted to those diseases due only to the tubercle bacillus by a formal resolution of the National Tuberculosis Association in 1923.²⁰ Thus no lesions could be called *tuberculosis* unless the bacillus was believed to be present even though it might be difficult or impossible to demonstrate it, nor could lesions with similar histopathologic features be called *tuberculous* if not caused by the tubercle bacillus.

The word *tubercular* has long been used as synonymous with *tuberculosis* in England and by many people in other countries, but in the United States the specific etiologic connotation has been confined to the latter term. For more than three quarters of a century the disease *tuberculosis* has been defined as any pathologic condition caused by the tubercle bacillus regardless of its manifestations.⁹

Diseases of the lung characterized by nodular or granular appearance, due to many different causes varying from simple inorganic silicosis, inanimate organic lipid pneumonia, various bacillary, spirochetal, fungal or animal caused diseases and many whose cause is still unknown, such as sarcoidosis or neoplasm, have been grouped together by Virchow and other writers under the name of granuloma.²⁵ The term *tubercular* has also been used for many years, as prescribed by the National Tuberculosis Association, to indicate nodular diseases of any cause, including tubercular leprosy, tubercular syphilis, sarcoid, or other conditions as well as tubercular tuberculosis.

Koch himself recognized that the tubercle bacillus is by no means the only acid-fast rod which might be discovered. The leprosy bacilli¹³ had been seen in tissues a decade before the discovery of the tubercle bacillus, and saprophytic acid-fast bacilli⁶ were found in a large variety of other sources soon after the discovery of the tubercle bacillus. Pathogenic acid-fast bacilli, such as were found to cause disease in cattle, birds and even cold-blooded animals were designated special types or varieties of tubercle bacilli even though their pathogenicity in man was questioned by Koch and many others for a long time.

Acid-fast bacilli different from the typical tubercle bacilli were found in a wide variety of other types of lesions in man besides those characteristic of tuberculosis, but in the past these appeared to be rare and were generally poorly described and documented. They were generally disregarded at the time when infection due to human type tubercle bacilli was practically universal and up to one-quarter of the human race had died from its effects.

With the widespread institutional segregation of vectors of tuberculosis and other public health measures during the past century, the incidence of disease due to typical human tubercle bacilli has rapidly diminished. The even more successful attack on tuberculosis in animals has led to similar decrease in the incidence of the bovine and avian tubercle bacilli. As a result, other kinds of acid-fast bacilli, even though unchanged in absolute incidence, now appear more often among positive cultures.¹

Increased interest in the susceptibility of the bacilli to various bacteriostatic agents, and in other differential characteristics, was stimulated by the introduction of specific chemotherapy. The changes in virulence and other properties of bacilli following unsuccessful isoniazid treatment and the introduction of new tests for pathogenicity and other characteristics have focused attention on such differences. As a result of this new knowledge and attitude, as well as of their relative frequency, "atypical," "anonymous" or other acid-fast bacilli differing from the typical human type bacillus are being increasingly reported.

A score of different strains of human type tubercle bacilli are now readily distinguishable from the much more common typical variety.⁵ All of these have positive reaction to the niacin test of Konno, which appears to be highly specific for human tubercle bacilli but is negative for all the other acid-fast bacilli.¹⁶ In the recent seventh edition of Bergey's "Manual of Determinate Bacteriology," only human type tubercle bacilli are included under the name of *Mycobacterium tuberculosis*.²¹ If we accept this nomenclature, the niacin test alone might separate out these organisms which are responsible for more than 95 per cent of all cases of pulmonary tuberculosis.

Many different kinds of mycobacteria besides the human tubercle bacilli, however, such as the bovine type bacillus, *Mycobacterium luciflavum*, avian tubercle bacilli, or the battey type bacilli may cause pulmonary disease indistinguishable from pulmonary tuberculosis due to the human type organisms.⁴ The vole bacillus and the numerous varieties associated with extrapulmonary lesions in man and warm and cold blooded animals, may not be implicated in ordinary pulmonary tuberculosis but may not be dismissed as saprophytes or nonpathogens.^{2,3} Many of these organisms were seen in earlier years but had been confused with typical tubercle bacilli; others had been considered to be harmless acid-fast saprophytes, more than a dozen different species of which have been recognized. Still others could not have been found with the methods then used.

Special culture media, with the addition of particular adjuvants which have been found important, or the omission of certain substances such as glycerine which inhibit some of these organisms; cultiva-

tion at different temperatures, especially below body temperature; growth at different pH, or under different gaseous tensions; and inoculation into a variety of animal hosts, not previously used, may facilitate the isolation of these organisms.

The differentiation and identification of the various kinds of acid-fast bacilli cannot be done by any single arbitrary criterion. The lesions produced in guinea pigs, rabbits and chickens by the human, bovine and avian type bacilli, respectively, are quite characteristic when present,²² but lack of virulence of the organisms in these animals by no means excludes the possibility of bacilli which are attenuated in this respect but which may still be pathogenic in man or other animals.

In general, slow-growing acid-fast bacilli which are not pigmented when grown in the dark are likely to be potential or actual pathogens, while fast-growing acid-fast bacilli, especially if non-pathogenic for mice, are usually saprophytes.⁸ There are, however, many exceptions. Some rapidly-growing acid-fast bacilli like *M. fortuitum*, abscessus, and *balnei* are undoubtedly pathogenic for man; and some slow-growing mycobacteria, like *M. orangeum*, the orange scotochrome, are undoubtedly saprophytic.

Similarly, absence of orange pigment, a positive reaction to neutral red test¹⁰ and strong cording¹⁸ are useful characteristics of tubercle bacilli. None of these characteristics, however, distinguish all pathogenic from the non-pathogenic forms of mycobacteria.¹² Thus the pathogenic *M. fortuitum*, *M. balnei* and *M. abscessus* are noncorded and are negative by the neutral red test, and the pathogenic *M. balnei*, *M. luciflavum* and *M. scrofulaceum* may produce abundant pigment, while some saprophytes, like *M. "radish"* may be neutral red positive or corded; and many, like *M. smegmatis*, are nonpigmented.

Consideration of colonial characteristics, the rate of growth, pigment production in the dark and after exposure to light and pathogenicity for mice and other animals will separate out most of the different strains of mycobacteria.²⁴ The identity of some cultures, however, may be difficult to establish without more extensive tests, including intensive study of cultural characteristics on a variety of media, the use of bacteriophage and various enzymes and susceptibility tests as well as animal inoculation.

Tubercle bacilli which have become attenuated for guinea pigs may still produce disease in mice and men. The consistent finding, in the discharges and tissues of human patients, of *M. luciflavum*, of *M. fortuitum*, of *M. ulcerans* and of other acid-fast bacilli which also produce progressive disease in experimental animals leaves little doubt of their virulence for man. Many of the lesions in which they are found, as well as those produced in animals,

are histologically indistinguishable from those due to typical tubercle bacilli.

In general, the pathogenic varieties of acid-fast bacilli are found in the discharges or lesions of animal or human hosts. Some of them have also been recovered from external sources, such as swimming tank water or surfaces, soil or sewage, or they may exist otherwise free in nature. Some of them found in such places may have been merely deposited there by human or animal hosts. Others may actually multiply freely outside of the body, but the finding of such forms is still quite infrequent.

The truly avirulent saprophytic varieties, on the other hand, may occasionally contaminate human or animal materials, in vivo or after leaving the body, or this may occur in the course of isolation. Much more often and readily, however, they may be found in other places, and this would occur even more often if more bacteriologic studies were made of waters, airs and places.

The number of cases of human disease caused by acid-fast bacilli other than the typical tubercle bacillus and leprosy is still too small, and insufficiently studied, to indicate the epidemiologic properties of the organisms. The differences in incidence in different areas is, however, suggestive of endemic foci of the diseases.¹⁷ Although the mode of transmission and the way they infect man have not been elucidated as yet, their association with human lesions, their bacteriological and pathological characteristics, and the nature of the lesions which they produce in experimental animals emphasize their close similarity to the tubercle bacillus.

The terms used for the designation of a disease are important, not only in identifying the condition and communicating knowledge about it, but also in bringing it under the terms of legislation and other arrangements which may be of practical significance. Acid-fast bacilli recovered from human materials are usually reported as tubercle bacilli by most laboratories, or are disregarded as saprophytes. When identification is attempted, and infection is reported as due to *M. luciflavum*, *M. fortuitum* or other less common varieties, the health department may not accept it as a diagnosis of *tuberculosis*. Thus subsidy is not given for the care of the patients and the usual public health measures may not be employed.

If the diagnosis were reported as due to *M. tuberculosis* of the bovine, avian, *luciflavum* or *fortuitum* variety, objection would be raised that the latest standard nomenclature of bacteriology does not recognize such terms, and that only the human bacillus may be called *M. tuberculosis*. It seems feasible, however, to report them as tubercle bacilli, although not *M. tuberculosis*, just as *Shigella sonnei* may be reported as dysentery bacilli but not as *S. dysenteriae*.

A diagnosis of *tuberculosis* rather than merely *mycobacterial granuloma*, or the euphemism *Koch's infection*, may be of importance both for good or for ill to the individual concerned and to his community. Not only may it facilitate recognition of the nature of the illness by the patient, and thus lead him to accept treatment, but it may entitle him to financial and social benefits, insurance, pensions, veteran's allowances and various official and unofficial services. The institution or community in which a patient lives may also profit not only from recognition of the presence of communicability for which precautions should be taken and are legally enforceable, but also in the receipt of specific state subsidies and other benefits which may depend on this diagnosis. On the other hand the social and financial losses, both to the individual and to the community, from the erroneous imposition of the diagnosis are obvious.

Whenever possible, however, the exact identity and characteristics of the acid-fast bacillus responsible for disease process should be determined. Not only may this help to establish the relationship of the organism to the disease but the clinical behavior and prognosis may vary in lesions due to different organisms. The finding of tubercle bacillus is generally recognized as an urgent indication for a study of all persons with whom the patient has been in contact, not only for the discovery of the possible source of the infection, but also for the discovery of other persons whom the patient may have infected. The finding of atypical acid-fast bacilli requires further study to determine whether these are variant forms of true tubercle bacilli or are other acid-fast bacilli which are also pathogenic, or are harmless saprophytes.

Epidemiologic study of the pathogenic acid-fast bacilli which are not tubercle bacilli is badly needed. The few reports so far available indicate a difference in the incidence of these organisms in different populations, but the exact mode of transmission and the possibility of animal vectors needs further investigation. The finding of *M. balnei* in skin lesions, for example, indicates specific measures in connection with swimming pools; if *M. avium* is found, special study of possible swine or fowl vectors is indicated; and if *M. orangeum* is present, water and other sources of laboratory contamination should be investigated.

The therapeutic implications of the identification of atypical acid-fast bacilli are also important. Not only are many of them resistant to drugs which are active against typical tubercle bacilli, but some of them are highly susceptible to sulfa drugs, to penicillin and to broad spectrum antibiotics which are ineffective against the human type bacillus. The dosages needed to give adequate concentrations of the drugs against these organisms may also differ.

Further study of the indications for other medical and surgical measures is needed. Individualization of treatment not only by patient but also by type of infecting organisms is here highly necessary.

As more and more is learned regarding the different kinds of tubercle bacilli and other acid-fast bacilli, greater and greater advances are to be expected in the prevention, diagnosis and treatment of the diseases which they may cause. The added burden on the laboratory in this differentiation may pay high dividends in the control of the granulomatous diseases.

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